REMARKS

Reconsideration and allowance are respectfully requested.

Claims 10-21 and 25-28 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. The scope of the claimed invention is not changed because the specific alcohols previously listed in claim 20 and presently deleted therefrom, are now listed in new claim 25. New claims 25-28 are similar to claims 20/21/25, but depend from a different independent claim.

Entry of the amendments is requested to address the Examiner's Section 112, second paragraph, rejection of claim 20 on pages 2-3 of the Office Action. They could not be earlier presented because the objection was initially raised in the final Office Action. Amendment of the claims will reduce the issues on appeal.

Applicants do not agree with the Examiners' contention in the Advisory Action that the claimed product "form I of (S)-(+)-Clopidogrel bisulfate" having a melting point of 184 ± 3°C is not supported by the previously submitted Rule 132 Declaration. Here, in order to secure allowance, Applicants propose a different amendment of the claims to require a melting point of 181 ± 3°C, which is consistent with the Rule 132 Declaration submitted on September 7, 2010 (see Experiment Nos. 1 to 3 therein). Note that its Experiment Nos. 4 and 5 show melting points outside the claimed range of 181 ± 3°C because they are meant to explain the fact that when chiral purity is compromised, a high melting point of form I of (S)-(+)-Clopidogrel bisulfate, i.e., between 205-212°C is observed (see paragraph 10 of the Rule 132 Declaration). Experiment Nos. 4 and 5 establish that when form I of (S)-(+)-Clopidogrel bisulfate having a melting point of about 212°C is obtained, chiral purity is decreased up to 19.56%. This clearly indicates that when chiral purity is compromised, the melting point of form I (S)-(+)-Clopidogrel bisulfate is increased ("The melting point goes up, if chiral purity is compromised").

To further support the inherent characteristic of melting temperature recited in the present claims (i.e., a melting point of 181 ± 3°C), additional Experiment Nos. 6 to 8 are attached hereto. They supplement experiments in the previously submitted Rule 132 Declaration and also show that the claimed product has a high chiral purity and an associated melting point in the range of 181-184°C.

Statement of the Substance of the Interview

In the telephonic interview on June 14, 2010, the Examiner suggested that Applicants submit a Rule 132 Declaration to establish (i) the melting point(s) of products that were made in the present application and (ii) the chiral purity of their structural (e.g., crystal) form I. The foregoing is Applicants' summary of the interview. If anything else is required to complete the record, do not hesitate to contact the undersigned.

35 U.S.C. 112 – Definiteness

Claims 10-21 were rejected under Section 112, second paragraph, as allegedly indefinite. Applicants traverse.

The Examiner objected to a limitation of the claimed process making a product having a melting point of 184 ± 3°C as new matter. In response to her suggestion, a Rule 132 Declaration was submitted on September 7, 2010 containing experimental data for chiral purity and melting point of form I of (S)-(+)-Clopidogrel bisulfate, which is a product prepared by the claimed process. The melting point is changed to 181 ± 3°C.

Claim 20 is amended to delete "such as"; claim 25 is added to list the deleted alcohols (i.e., specific alcohols or mixtures thereof) as solvents.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 112 – Written Description

Claims 10-18 and 21 were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse.

The Examiner objected to "form I of (+)-(S)-clopidogrel bisulfate which has a melting point of 181 ± 3°C" because of a lack of purity and melting point data. Here, no dispute exists that form I of (S)-(+)-Clopidogrel bisulfate was prepared according to the claimed process. Its purity and melting point are inherent properties of the product made by the process described in the present specification. Therefore, a Rule 132 Declaration was submitted on September 7, 2010 containing chiral purity and melting point data.

Claims 14-19 were also rejected under Section 112, first paragraph, as allegedly adding new matter. Applicants traverse because an amendment introducing an inherent

characteristic into the claims is not prohibited by the written description requirement. See *In re Smythe*, 178 USPQ 279, 285 (C.C.P.A. 1973).

As discussed above, inserting an inherent property such as melting point does not add new matter to the disclosure.

Withdrawal of the written description rejections is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date.

35 U.S.C. 112 – Enablement

Claims 10-21 were rejected under Section 112, first paragraph, as allegedly failing to comply with the enablement requirement for the making of polymorphic forms. Applicants traverse because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

The processes taught by Applicants in their specification enables the claimed invention. All the solvents shown in the present examples lead to the formation of form I, and any person skilled in the art can practice the invention using the guidance in Applicants' specification. By contrast, there is no evidence of record that production of form I involves any specific temperature, time, or other reaction conditions. The Examiner's example of the production of polymorphic forms of ammonium nitrate is not probative of the different reaction claimed herein. Thus, if this rejection is maintained, the Examiner is respectfully requested to provide acceptable evidence or reasoning that is inconsistent with (and contradicts) the teachings in the present specification.

The Examiner objected that the present specification describes a limited number of examples, and alleged that the process of preparing "form I" is very specific. But a specification need not teach, and preferably omits, what is well known in the art. See *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986). were disclosed. Here, a Rule 132 Declaration is submitted herewith containing additional synthetic reactions, which prepare form I of (S)-(+)-Clopidogrel bisulfate, under conditions within the scope of the claimed invention. They demonstrate that the allegation that "such process of making 'Form I' is very specific and any change may produce other forms" (page 6 of the Office Action) is incorrect.

Withdrawal of the enablement rejection is requested because it would not require undue experimentation for a person of skill in the art to practice the claimed invention.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 10-11 were rejected under Section 102(b) as allegedly anticipated by Bousquet et al. (U.S. Patent 6,429,210). Applicants traverse.

Applicants' claimed invention requires treating Clopidogrel base (as such or derived from Clopidogrel bisulfate or Clopidogrel camphor sulfonate) with dilute or concentrated H_2SO_4 in one or more solvents, at least of which is an alcohol. As noted by the Examiner, however, Bousquet discloses use of acetone, which is not an alcohol. Therefore, processes according to claims 10-11 are novel.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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Experiment No. 6

In a round bottom flask, (200 gm) Clopidogrel base was taken in 1000ml of n-hexanol. Cool the reaction mass to 10-15 °C; subsequently add 4.1 ml of water. Concentrated sulphuric acid (59.2 gm) was added to reaction mass dropwise at 10-15 °C. Warm the reaction mass to 20-25°C. The reaction mixture was seeded with 30mg of clopidogrel hydrogen sulfate form 1 and stirred for 20 hour at temperature 20-25°C. The solid was filtered and dried. A solid white Clopidogrel bisulfate form 1 is obtained

Yield: 250gm (95%) HPLC purity: 98.25 %, Chiral purity: 99.50 %,

Melting point: 181-184 °C.

XRD- Complies with diffractogram of standard Form 1 of Clopidogrel bisulfate and represented as Fig. 6

Experiment No. 7

In a round bottom flask, (200 gm) Clopidogrel base was taken in 1000ml of n-hexanol. Cool the reaction mass to 10-15 °C; subsequently add 4.1 ml of water. Concentrated sulphuric acid (59.2 gm) was added to reaction mass dropwise at 10-15 °C. Warm the reaction mass to 20-25°C. The reaction mixture was seeded with 30mg of clopidogrel hydrogen sulfate form 1 and stirred for 20 hour at temperature 20-25°C. The solid was filtered and dried. The dried sample was further stirred in MTBE (750 ml) for 10 min. A solid white Clopidogrel bisulfate form 1 is obtained.

Yield: 233gm (89%) HPLC purity: 99.25%, Chiral purity: 99.73 %,

Melting point: 182-185°C.

XRD- Complies with diffractogram of standard Form 1 of Clopidogrel bisulfate and represented as Fig. 7.

Experiment No. 8

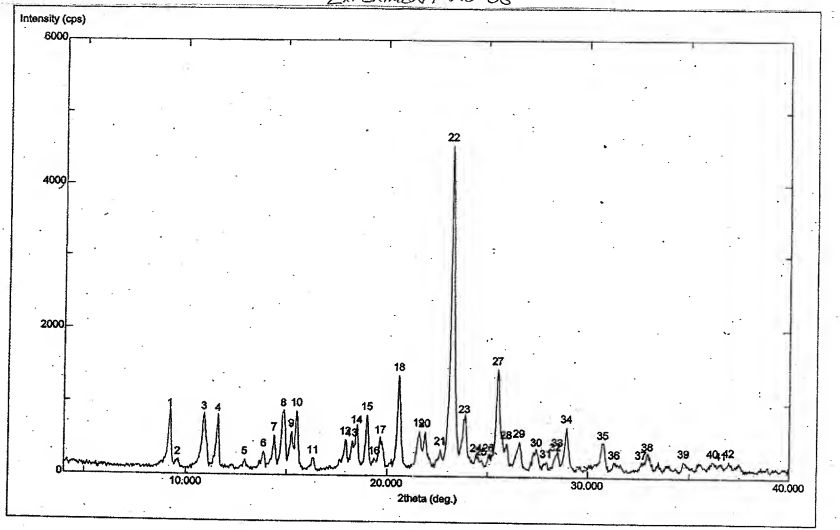
In a round bottom flask, (100 gm) Clopidogrel base was taken in 500 ml of dodecanol. The reaction mixture was stirred at 50-55 °C for 10 minutes to obtain a clear solution. Cool the reaction mass to 20 °C; subsequently add 2 ml of water. The reaction mixture was seeded with 1 gm of clopidogrel hydrogen sulfate form 1 and (29 gm) sulphuric acid added dropwise to reaction mass at 25-30°C in 15-20 min. Warm the reaction mixture to 44-45 °C temperature. The reaction mass was stirred for 6 hour at temperature 44-45 °C, filtered, washed with MTBE and dried. A solid white Clopidogrel bisulfate form 1 is obtained.

Yield: 91gm (61%) HPLC purity: 99.06 %, Chiral purity: 98.91%,

Melting point: 181-183 °C.

XRD- Complies with diffractogram of standard Form 1 of Clopidogrel bisulfate and represented as Fig. 8.

EXPERIMENT No-06



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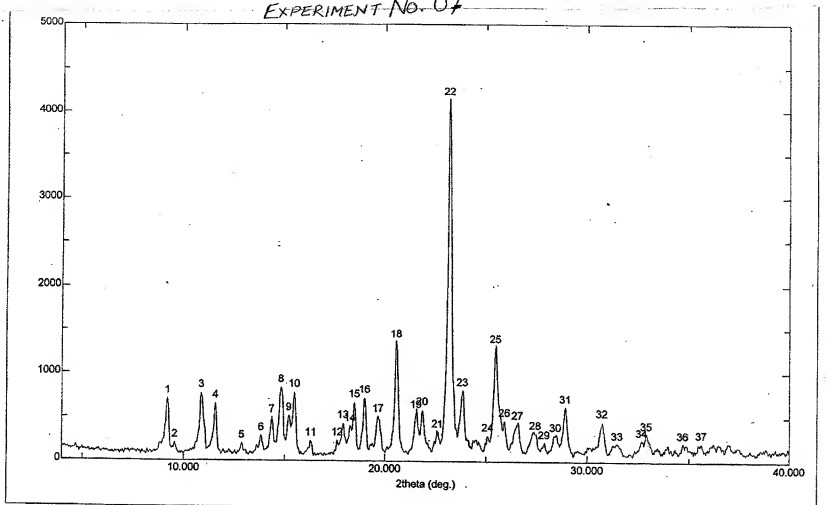

EXPERIMENT No. 08